Remarks

I. Status of the Claims

Upon entry of the foregoing amendment, claims 167-229 and 231-234 are pending in the application, with claims 167, 170, 184, 188, 191, 197, 200, 203, 206, 209, and 213 being the independent claims. Claim 230 has been canceled without prejudice to or disclaimer of the subject matter therein. These changes are believed to introduce no new matter, and their entry is respectfully requested.

II. The Amendments

Claim 230 has been canceled. Claims 167, 170, 197 and 200 have been amended *to specify that the glycoengineering involves the genetic manipulation of the host cell.* Support for this amendment can be found, *inter alia*, in the application as filed at page 7, lines 24-26, and in claim 230, which is now canceled. The remaining amendments are all merely formal or typographical in nature. Accordingly, no new matter is believed to have been added by these amendments, and their entry is respectfully requested.

III. The Rejections

A. The Rejection Under 35 U.S.C. § 103(a)

At page 2 of the Office Action, claims 167-173, 175, 177, 179, 197-202, 218-229 and 231-234 have been rejected as being obvious over Rothman, R.J. *et al.*, *Mol. Immunol. 26*:1113-1123 (1989)("Rothman") in view of U.S. Pat. No. 6,183,744 to Goldenberg. Rothman is cited as teaching a method for producing a full-length antibody having increased Fc mediated cellular cytotoxicity or increased Fc receptor binding affinity by culturing a host cell expressing an antibody in the presence of certain

glycosylation and carbohydrate processing inhibitors. Goldenberg is cited as generally teaching methods of making and using recombinant monoclonal antibodies. According to the Examiner, one of ordinary skill in the art seeking to generate improved recombinant therapeutic antibodies for the treatment of cancer and other malignancies, such as those of Goldenberg, would have been motivated to use the method of Rothman to produce recombinant antibodies with enhanced Fc mediated antibody-dependent cytotoxicity mediated by natural killer cells, and would have had a reasonable expectation of success in doing so. The Examiner further states that it must be *assumed* that the activity of glycosyltransferases such as α-mannosidase II, β(1,4)-N-acetylglucosaminyltransferase III and β(1,4)-galactosyltransferase is necessarily decreased in the methods of Rothman.

Applicants respectfully traverse the rejection.

As an initial matter, Applicants point out that the Examiner's reliance on Rothman as inherently teaching the decreased activity of α-mannosidase II, β(1,4)-N-acetylglucosaminyltransferase III and β(1,4)-galactosyltransferase is improper. Although Rothman attempts to characterize the structural alterations in glycosylation induced by Cs, Mon and Sw, no attempt is made to link the structural alterations to particular effects of the various inhibitors on the specific enzymes mentioned above. In order for the Examiner to rely on an inherent teaching of a reference, that teaching must be shown to *necessarily flow* from the explicit teachings of the reference. In this case, however, Rothman does not definitively link any of the inhibitors of glycosylation and carbohydrate processing to decreased activity of the particular enzymes recited in the

claims. Accordingly, it is improper for the Examiner to assume that such a decrease is necessarily occurring.

In addition, without acquiescing in the propriety of the rejection and solely in the interests of advancing prosecution, Applicants have amended claims 167, 170, 197 and 200 to recite that the glycoengineering comprises *genetically manipulating the host cell* to alter the activity of at least one glycoprotein-modifying glycosyl transferase. Neither Rothman nor Goldenberg discloses this feature of the amended claims. Rather, as noted by the Examiner, the "glycoengineering" in Rothman involves culturing antibody-producing cells in the presence of glycosylation and carbohydrate processing inhibitors. This type of metabolic engineering is fundamentally different from the glycoengineering recited in the amended claims, which involves the genetic manipulation of the oligosaccharide synthesis pathways of the host cell to achieve the desired antibody glycoforms. Rothman does not in any way suggest that the claimed genetic manipulation is either possible or desirable. Indeed, Rothman does not even attempt to link the inhibitors used to any effects on particular glycoprotein-modifying glycosyl transferases, much less suggest how to genetically manipulate glycosyltransferase activity to achieve the desired increases in ADCC. Goldenberg is simply relied on for teaching methods of making and using recombinant monoclonal antibodies, and thus does not compensate for the deficiencies of Rothman. Accordingly, Applicants respectfully submit that the rejection of claims 167-173, 175, 177, 179, 197-202, 218-229 and 231-234 as being obvious over Rothman in view of Goldenberg has been obviated, and should be withdrawn.

The Examiner has also rejected claim 216 as obvious over Rothman in view of Goldenberg and further in view of U.S. Pat. No. 5,939,068 to Brams *et al.* Brams *et al.* is cited only for teaching the preferential use of CHO cells for expressing recombinant antibodies. As noted above, neither Rothman nor Goldenberg teaches or suggests genetically manipulating a host cell to alter the activity of a glycoprotein-modifying glycosyl transferase, which is a feature of the amended claims. Accordingly, the rejection of claim 216 is also obviated, and should be withdrawn.

B. The Rejections for Obviousness-Type Double Patenting

At pages 6-8 of the Office Action, claims 170-234 and 167-234 have been *provisionally* rejected for obviousness-type double patenting over claims 228-260 of U.S. Appl. No. 10/761,435 and claims 159-167 of U.S. Appl. No. 10/633,699, respectively. Applicants respectfully traverse this rejection.

Applicants again point out that the present application was filed on August 5, 2003, and claims priority to U.S. Appl. No. 09/294,584, filed April 20, 1999. Co-pending U.S. Appl. No. 10/761,435, was filed on January 22, 2004. Therefore, the present application is the earlier-filed of the two pending applications. According to the Manual of Patent Examining Procedure:

> If a "provisional" nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer.

M.P.E.P. § 804(I)(B)(1). Like the present application, U.S. Appl. No. 10/633,699 also claims priority to U.S. Appl. No. 09/294,584. In the Restriction Requirement that issued in the `584 application on September 26, 2000 (copy attached as Exhibit A), the claims

drawn to methods for glycoengineering host cells to produce a modified polypeptides, such as antibodies (e.g., claim 32) were restricted by the Office to a distinct group (Group II) from the claims directed to the antibodies produced by those methods (e.g., claims 75-85) (Groups III-IX) (copy of as filed claims from `584 application attached as Exhibit B). Group II was elected for further prosecution in the `584 application, whereas the antibody claims were pursued in U.S. Appl. No. 10/633,699. Thus, the present application and the `699 application are related as a continuation and a divisional, respectively, of parent U.S. Appl. No. 09/294,584. Accordingly, the rejection of the present claims over the claims of copending U.S. Appl. No. 10/633,699 is improper under 35 U.S.C. § 121, and should be withdrawn.

As the obviousness rejections have been overcome for the reasons noted above, and because the obviousness-type double patenting rejection over 10/633,699 is improper under 35 U.S.C. § 121, Applicants respectfully submit that the rejection over 10/761,435 should be withdrawn in accordance with M.P.E.P. § 804(I)(B)(1). All claims are thus in condition for allowance.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will

expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Timothy J. Shea, Jr.
Attorney for Applicants
Registration No. 41,306

Date: January 26, 2009

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Washington, D.C. 20005-3934
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922164_1.DOC

Exhibit A

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/294,584	04/20/99	UMANA	P 9187-0016-99

HM12/0926

PENNIE & EDMONDS
1155 AVENUE OF THE AMERICAS
NEW YORK NY 10036-2711

EXAMINER	
SANDALS, W	
ART UNIT	PAPER NUMBER
1636	9

DATE MAILED: 09/26/00

Response to restriction Requirement - 10/26/00 WS

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

DOCKETED Restriction Response October 26, 2000
Stat Bar March 26, 2001

REFERRED TO
REC'D
SEP 28 2000
Pennie & Edmonds
O.K. for filing

PTO-90C (Rev. 2/95)

2 - Mail Copy

Office Action Summary

Application No.	Applicant(s)
09/294,584	Umana et al.
Examiner	**Group Art Unit**
WILLIAM SANDALS	1636

☒ Responsive to communication(s) filed on *Jul 19, 2000*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *1* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-87* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☐ Claim(s) _____ is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims *1-87* are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☒ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Response to Arguments

1. The previous restriction requirement did not properly address the groupings of the claims, and pursuant to a discussion of the restriction with Applicant's representative, it has been determined to repeat the restriction requirement with the inclusion of the correction of the groupings of the claims, and a deletion of the species election requirement.

Election/Restriction

2. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-10, 86 and 87, drawn to a host cell with a nucleic acid encoding a glycosyl transferase, classified in class 435, subclass 325.

II. Claims 11-24, 28-35 and 39-73, drawn to a host cell with a nucleic acid encoding a glycosyl transferase and a nucleic acid encoding an antibody, and a method of making the host cell, classified in class 435, subclass 326.

III. Claims 25, 36 and 75, drawn to a C2B8 antibody, classified in class 530, subclass 387.1.

IV. Claim 26, 37 and 76, drawn to ChCe7 antibody, classified in class 530, subclass 387.1.

V. Claim 27, 38 and 77, drawn to chG250 antibody, classified in class 530, subclass 387.1.

VI. Claim 78, drawn to anti-HER-2 antibody, classified in class 350, subclass 378.1.

VII. Claim 79, drawn to ING-1 antibody, classified in class 350, subclass 378.1.

VIII. Claim 80, drawn to 362W94 antibody, classified in class 530, subclass 378.1.

IX. Claim 81, drawn to SF-25 antibody, classified in class 530, subclass 378.1.

X. Claim 82, drawn to A33 antibody, classified in class 530, subclass 378.1.

XI. Claim 83, drawn to R24 antibody, classified in class 530, subclass 387.1.

3. The inventions are distinct, each from the other because of the following reasons: Inventions of Groups I and II are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions of Groups I and II are unrelated because a host cell which contains a nucleic acid encoding a glycosyl transferase is not biologically or biochemically related to a host cell which contains a nucleic acid encoding a glycosyl transferase and a nucleic acid encoding an antibody. A host cell encoding a glycosyl transferase may be a host cell which is distinct and unique from a host cell with a nucleic acid encoding an antibody, and host cells with nucleic acids encoding an antibody may not have a nucleic acid encoding a glycosyl transferase.

4. Inventions of Groups I and III-XI or II and III-XI are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different

modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions of Groups III-XI are distinct and unique antibodies which are biologically, and biochemically unique and are patentably distinct, and the antibodies of Groups III-XI are distinct from the methods of Group II.

5. Because these inventions are distinct for the reasons given above and the search required for Group I or Group II is not required for Groups III-XI, restriction for examination purposes as indicated is proper.

6. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

7. Currently, claims 74, 84 and 85 are generic to any of the groups III-XI, claims 25-27, 36-38 and 75-83. If any of Groups III-XI are elected, then claims 74, 84 and 85 will be examined as they apply to the elected claims.

8. A telephone call was made to Birgit Milauer on September 19, 2000 to request an oral election to the above restriction requirement, but did not result in an election being made. Ms Milauer indicated that the application is being transferred to another representative, and that the election could not be made at this time.

9. Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

10. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Conclusion

11. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Friday from 8:30 AM to 5:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott can be reached at (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Receptionist, whose telephone number is (703) 308-0196.

William Sandals, Ph.D.
Examiner
September 22, 2000

ROBERT A. SCHWARTZMAN
PRIMARY EXAMINER

Interview Summary

Application No.	Applicant(s)
09/294,584	Umana et al.
Examiner	**Group Art Unit**
WILLIAM SANDALS	1636

All participants (applicant, applicant's representative, PTO personnel):

(1) *WILLIAM SANDALS* (3) _____

(2) *Birgit Milauer, Esq.* (4) _____

Date of Interview *Sep 19, 2000*

Type: ☒ Telephonic ☐ Personal (copy is given to ☐ applicant ☐ applicant's representative).

Exhibit shown or demonstration conducted: ☐ Yes ☒ No. If yes, brief description:

Agreement ☐ was reached. ☒ was not reached.

Claim(s) discussed: *1-87*

Identification of prior art discussed:
None

Description of the general nature of what was agreed to if an agreement was reached, or any other comments:
We discussed the restriction requirement. Since the application is being transferred to a different representative, no election was made.

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendents which would render the claims allowable is available, a summary thereof must be attached.)

1. ☒ It is not necessary for applicant to provide a separate record of the substance of the interview.

Unless the paragraph above has been checked to indicate to the contrary, A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a response to the last Office action has already been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW.

2. ☐ Since the Examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action. Applicant is not relieved from providing a separate record of the interview unless box 1 above is also checked.

Examiner Note: You must sign and stamp this form unless it is an attachment to a signed Office action.

CLAIMS

What is claimed is:

1. A host cell engineered to express at least one nucleic acid encoding a glycoprotein-modifying glycosyl transferase at a regulated level.

2. The host cell of Claim 1, wherein a nucleic acid molecule comprising at least one gene encoding a glycoprotein-modifying glycosyl transferase has been introduced in said host cell.

3. The host cell of Claim 1, wherein said host cell has been engineered such that an endogenous glycoprotein-modifying glycosyl transferase is activated.

4. The host cell of Claim 2 or 3, wherein said host cell is a CHO cell, a BHK cell, a NS0 cell, a SP2/0 cell, or a hybridoma cell.

5. The host cell of Claim 3, wherein said endogenous glycoprotein-modifying glycosyl transferase has been activated by insertion of a regulated promoter element into the host cell chromosome.

6. The host cell of Claim 2 or 3, wherein said glycoprotein-modifying glycosyl transferase is GnT III, GnT V, Man II, or Gal T.

7. The host cell of Claim 2 or 3, wherein said host cell is engineered to express at least two different glycoprotein-modifying glycosyl transferases selected from the group consisting of GnT III, GnT V, Man II, and Gal T.

8. The host cell of Claim 7, wherein at least one gene encoding a glycoprotein-modifying glycosyl transferase is operably linked to a constitutive promoter element.

9. The host cell of Claim 2, wherein at least one gene encoding a

glycoprotein-modifying glycosyl transferase is operably linked to a regulated promoter element.

10. The host cell of Claim 5 or 9, wherein the regulated promoter element is a tetracycline-regulated promoter system, an ecdysone-inducible promoter system, a lac-switch promoter system, a glucocorticoid-inducible promoter system, a temperature-inducible promoter system, or a metallothionein metal-inducible promoter system.

11. A host cell engineered to express at least one nucleic acid molecule encoding a glycoprotein-modifying glycosyl transferase, wherein said host cell is capable of producing a protein having enhanced Fc-mediated cellular cytotoxicity.

12. The host cell of Claim 11, wherein said protein is a whole antibody molecule, an antibody fragment, or a fusion protein that includes a region equivalent to the Fc region of an immunoglobulin.

13. The host cell of Claim 12, wherein a nucleic acid molecule comprising at least one gene encoding a glycoprotein-modifying glycosyl transferase has been introduced in said host cell.

14. The host cell of Claim 12, wherein said host cell has been selected to carry a mutation triggering expression of an endogenous glycoprotein-modifying glycosyl transferase.

15. The host cell of Claim 14, wherein said host cell is the mutant lec10.

16. The host cell of Claim 12, wherein said host cell has been engineered such that an endogenous glycoprotein-modifying glycosyl transferase is activated.

17. The host cell of Claim 16, wherein said endogenous glycoprotein-modifying glycosyl transferase has been activated by insertion of a regulated promoter element into the host cell chromosome.

18. The host cell of Claim 16, wherein said endogenous glycoprotein-modifying glycosyl transferase has been activated by insertion of a constitutive promoter element, a transposon, or a retroviral element into the host cell chromosome.

19. The host cell of Claim 11 or 13, further comprising at least one transfected nucleic acid encoding an antibody molecule, an antibody fragment, or a fusion protein that includes a region equivalent to the Fc region of an immunoglobulin.

20. The host cell of Claim 13, wherein at least one gene encoding a glycoprotein-modifying glycosyl transferase is operably linked to a constitutive promoter element.

21. The host cell of Claim 13, wherein at least one gene encoding a glycoprotein-modifying glycosyl transferase is operably linked to a regulated promoter element.

22. The host cell of Claim 21, wherein the regulated promoter element is a tetracycline-regulated promoter system, an ecdysone-inducible promoter system, a lac-switch promoter system, a glucocorticoid-inducible promoter system, a temperature-inducible promoter system, or a metallothionein metal-inducible promoter system.

23. The host cell of Claim 11, wherein said host cell is a hybridoma cell.

24. The host cell of Claim 11, wherein said engineered host cell is an engineered CHO cell, an engineered BHK cell, an engineered NS0 cell, or an engineered SP2/0 cell.

25. The host cell of Claim 11, wherein said host cell comprises at least one transfected nucleic acid encoding a chimeric anti-CD20 monoclonal antibody (C2B8).

26. The host cell of Claim 11, wherein said host cell comprises at least one transfected nucleic acid encoding a chimeric anti-human neuroblastoma monoclonal

antibody (chCE7).

27. The host cell of Claim 11, wherein said host cell comprises at least one transfected nucleic acid encoding a chimeric anti-human renal cell carcinoma monoclonal antibody (ch-G250), a humanized anti-HER2 monoclonal antibody, a chimeric anti-human colon, lung, and breast carcinoma monoclonal antibody (ING-1), a humanized anti-human 17-1A antigen monoclonal antibody (3622W94), a humanized anti-human colorectal tumor antibody (A33), an anti-human melanoma antibody (R24) directed against GD3 ganglioside, or a chimeric anti-human squamous-cell carcinoma monoclonal antibody (SF-25).

28. The host cell of Claim 11, wherein at least one nucleic acid molecule encodes ß(1,4)-N-acetylglucosaminyltransferase III (GnT III).

29. The host cell of Claim 28, further comprising at least one nucleic acid encoding a ß(1,4)-galactosyl transferase (GalT).

30. The host cell of Claim 28, further comprising at least one nucleic acid encoding a mannosidase II (Man II).

31. The host cell of Claim 28, further comprising at least one nucleic acid encoding a β(1,4)-galactosyl transferase (GalT) and at least one nucleic acid encoding a mannosidase II (Man II).

32. A method for producing a protein compound having enhanced Fc-mediated cellular cytotoxicity in a host cell, comprising:

(a) providing a host cell engineered to express a glycoprotein-modifying glycosyl transferase at a regulated level, chosen to improve glycosylation of a protein compound of interest, wherein said host cell expresses at least one nucleic acid encoding an antibody, an antibody fragment, or a fusion protein that includes a region equivalent to the Fc region of an immunoglobulin;

(b) culturing said host cell under conditions which permit the production of said protein compound having enhanced Fc-mediated cellular

cytotoxicity; and

(c) isolating said protein compound having enhanced Fc-mediated cellular cytotoxicity.

33. The method of Claim 32, wherein in step (a), said host cell comprises at least one nucleic acid encoding a whole antibody.

34. The method of Claim 32, wherein in step (a), said host cell comprises at least one nucleic acid encoding an antibody fragment.

35. The method of Claim 32, wherein in step (a), said host cell comprises at least one nucleic acid encoding a fusion protein comprising a region resembling a glycosylated Fc region of an immunoglobulin.

36. The method of Claim 32, wherein said host cell comprises at least one transfected nucleic acid encoding a chimeric anti-CD20 monoclonal antibody (C2B8).

37. The method of Claim 32, wherein said host cell comprises at least one transfected nucleic acid encoding a chimeric anti-human neuroblastoma monoclonal antibody (chCE7).

38. The method of Claim 32, wherein said host cell comprises at least one transfected nucleic acid encoding a chimeric anti-human renal cell carcinoma monoclonal antibody (ch-G250), a humanized anti-HER2 monoclonal antibody, a chimeric anti-human colon, lung, and breast carcinoma monoclonal antibody (ING-1), a humanized anti-human 17-1A antigen monoclonal antibody (3622W94), a humanized anti-human colorectal tumor antibody (A33), an anti-human melanoma antibody (R24) directed against GD3 ganglioside, or a chimeric anti-human squamous-cell carcinoma monoclonal antibody (SF-25).

39. The method of Claim 32, wherein at least one gene encoding a glycoprotein-modifying glycosyl transferase has been introduced into said host cell.

40. The host cell of Claim 32, wherein said host cell has been selected to carry a mutation triggering expression of an endogenous glycoprotein-modifying glycosyl transferase.

41. The host cell of Claim 40, wherein said host cell is the mutant lec10.

42. The host cell of Claim 32, wherein said host cell has been engineered such that an endogenous glycoprotein-modifying glycosyl transferase is activated.

43. The method of Claim 32, wherein said glycosyl transferase is a ß(1,4)-N-acetylglucosaminyltransferase III (GnT III).

44. The method of Claim 43, wherein said GnT III is expressed using a constitutive promoter system.

45. The method of Claim 43, wherein said GnT III is expressed using a regulated promoter system.

46. The method of Claim 45, wherein said regulated promoter system is a tetracycline-regulated promoter system, an ecdysone-inducible promoter system, a lac-switch promoter system, a glucocorticoid-inducible promoter system, a temperature-inducible promoter system, or a metallothionein metal-inducible promoter system.

47 The method of Claim 32, wherein said glycosyl transferase is a β(1,4)-galactosyl transferase (GalT).

48. The method of Claim 47, wherein said GalT is expressed using a constitutive promoter system.

49. The method of Claim 47, wherein said GalT is expressed using a regulated promoter system.

50. The method of Claim 49, wherein said regulated promoter system is

a tetracycline-regulated promoter system, an ecdysone-inducible promoter system, a lac-switch promoter system, a glucocorticoid-inducible promoter system, a temperature-inducible promoter system, or a metallothionein metal-inducible promoter system.

51. The method of Claim 32, wherein said host cell is engineered to express a plurality of nucleic acids encoding a glycoprotein-modifying glycosyl transferase at a regulated level, chosen to improve glycosylation of a protein compound of interest, wherein at least one nucleic acid encodes GnT III and at least one nucleic acid encodes a β(1,4)-galactosyl transferase (GalT).

52. The host cell of Claim 51, wherein a nucleic acid molecule comprising at least one gene encoding a glycoprotein-modifying glycosyl transferase has been introduced into said host cell.

53. The host cell of Claim 51, wherein said host cell has been selected to carry a mutation triggering expression of at least one endogenous glycoprotein-modifying glycosyl transferase.

54. The host cell of Claim 51, 52, or 53, wherein said host cell has been engineered such that an endogenous glycoprotein-modifying glycosyl transferase is activated.

55. The method of Claim 32, wherein said host cell comprises a plurality of nucleic acids encoding a glycoprotein-modifying glycosyl transferase at a regulated level, chosen to improve glycosylation of a protein compound of interest, wherein at least one nucleic acid encodes GnT III and at least one nucleic acid encodes a mannosidase II (Man II).

56. The host cell of Claim 55, wherein a nucleic acid molecule comprising at least one gene encoding a glycoprotein-modifying glycosyl transferase has been introduced into said host cell.

57. The host cell of Claim 55, wherein said host cell has been selected to

carry a mutation triggering expression of at least one endogenous glycoprotein-modifying glycosyl transferase.

58. The host cell of Claim 55, 56, or 57, wherein said host cell has been engineered such that an endogenous glycoprotein-modifying glycosyl transferase is activated.

59. The method of Claim 32, wherein said host cell comprises a plurality of nucleic acids encoding a glycoprotein-modifying glycosyl transferase at a regulated level, chosen to improve glycosylation of a protein of interest, wherein at least one nucleic acid encodes GnT III, at least one nucleic acid encodes β(1,4)-galactosyl transferase (GalT), and at least one nucleic acid encodes mannosidase II (Man II).

60. The host cell of Claim 59, wherein a nucleic acid molecule comprising at least one gene encoding a glycoprotein-modifying glycosyl transferase has been introduced into said host cell.

61. The host cell of Claim 59, wherein said host cell has been selected to carry a mutation triggering expression of at least one endogenous glycoprotein-modifying glycosyl transferase.

62. The host cell of Claim 59, 60, or 61, wherein said host cell has been engineered such that an endogenous glycoprotein-modifying glycosyl transferase is activated.

63. The method of Claim 32, wherein the expression level of at least one glycoprotein-modifying glycosyl transferase has been selected to produce an antibody molecule, an antibody fragment, or a fusion protein that includes a region equivalent to the Fc region of an immunoglobulin having enhanced Fc-mediated cellular cytotoxicity at a higher level than the Fc-mediated cellular cytotoxicity obtained from a different expression level of the same glycosyl transferase gene.

64. The method of Claim 63, wherein said expression levels are

determined by Western blot analysis using a glycosyl transferase-specific antibody.

65. The method of Claim 63, wherein said expression levels are determined by Northern blot analysis using a glycosyl transferase-specific probe.

66. The method of Claim 63, wherein said expression levels are determined by measuring the enzymatic activity of glycosyl transferase.

67. The method of Claim 63, wherein said expression levels are determined using a lectin which binds to biosynthetic products of glycoprotein-modifying glycosyl transferase.

68. The method of Claim 67, wherein the lectin is E_4-PHA lectin.

69. The method of Claim 63, wherein said nucleic acid encoding said glycoprotein-modifying glycosyl transferase is operatively linked to a reporter gene, and wherein said expression levels of said glycosyl transferase are determined by measuring a signal correlated with the expression level of said reporter gene.

70. The method of Claim 69, wherein said reporter gene is transcribed together with at least one nucleic acid encoding said glycoprotein-modifying glycosyl transferase as a single RNA molecule and their respective coding sequences are linked either by an internal ribosome entry site (IRES) or by a cap-independent translation enhancer (CITE).

71. The method of Claim 69, wherein said reporter gene is translated together with at least one nucleic acid encoding said glycoprotein-modifying glycosyl transferase such that a single polypeptide chain is formed.

72. The method of Claim 63, wherein said nucleic acid encoding said glycoprotein-modifying glycosyl transferase is operatively linked to a reporter gene under the control of a single promoter, wherein said nucleic acid encoding said glycoprotein-modifying glycosyl transferase and said reporter gene are transcribed into

an RNA molecule which is alternatively spliced into two separate messenger RNA (mRNA) molecules, wherein one of the resulting mRNAs is translated into said reporter protein, and the other is translated into said glycoprotein-modifying glycosyl transferase.

73. The method of Claim 32, wherein said host cell further comprises a nucleic acid encoding a glycosidase.

74. An antibody having enhanced antibody dependent cellular cytotoxicity (ADCC) produced by the host cells of Claim 11.

75. A chimeric anti-CD20 monoclonal antibody (C2B8) having enhanced antibody dependent cellular cytotoxicity (ADCC) produced by the host cells of Claim 25.

76. A chimeric anti-human neuroblastoma monoclonal antibody (chCE7) having enhanced antibody dependent cellular cytotoxicity (ADCC) produced using the host cells of Claim 26.

77. A chimeric anti-human renal cell carcinoma monoclonal antibody (ch-G250) having enhanced antibody dependent cellular cytotoxicity (ADCC) produced using the host cells of Claim 27.

78. A humanized anti-HER2 monoclonal antibody having enhanced antibody dependent cellular cytotoxicity (ADCC) produced using the host cells of Claim 27.

79. A chimeric anti-human colon, lung, and breast carcinoma monoclonal antibody (ING-1) having enhanced antibody dependent cellular cytotoxicity (ADCC) produced using the host cells of Claim 27.

80. A humanized anti-human 17-1A antigen monoclonal antibody (3622W94) having enhanced antibody dependent cellular cytotoxicity (ADCC)

produced using the host cells of Claim 27.

81. A chimeric anti-human squamous-cell carcinoma monoclonal antibody (SF-25) having enhanced antibody dependent cellular cytotoxicity (ADCC) produced using the host cells of Claim 27.

82. A humanized anti-human colorectal tumor antibody (A33), having enhanced antibody dependent cellular cytotoxicity (ADCC) produced using the host cells of Claim 27.

83. An anti-human melanoma antibody (R24) directed against GD3 ganglioside, having enhanced antibody dependent cellular cytotoxicity (ADCC) produced using the host cells of Claim 27.

84. An antibody fragment that includes a region equivalent to the Fc region of an immunoglobulin, having enhanced Fc-mediated cellular cytotoxicity produced using the host cells of Claim 11.

85. A fusion protein that includes a region equivalent to the Fc region of an immunoglobulin, having enhanced Fc-mediated cellular cytotoxicity produced using the host cells of Claim 11.